REMARKS

Claims 1-18 are all the claims pending in the application. Claims 14 and 15 are withdrawn from consideration. Claims 1-13 and 16-18 are rejected.

Withdrawn claim 14 is amended to depend from claim 1 rather than claim 13.

Claim 18 is amended to again recite that the C_{1-6} alkyl group represented by R^{26} and R^{27} can be substituted with a halogen atom.

No new matter is added.

A. Election/Restrictions

Claims 14-15 are withdrawn from consideration as being directed to a non-elected invention.

Pursuant to 37 C.F.R. § 1.475(b) and MPEP § 821.04(b), the Examiner is requested, respectfully, to rejoin the method claims upon an indication that the product claims are allowable.

B. Claim Rejections - 35 USC § 102

The rejection of claim 18 under 35 U.S.C. § 102(b) as being anticipated by Yuasa et al. (Relative Nucleophilicity of the Two Sulfur Atoms in 1,5-Dithioglucopyranoside", Angewandte Chemie, Internation Edition in English, 36(8), pp. 868-870, 1997) is maintained for reasons of record.

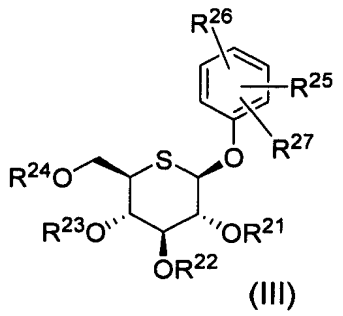
The Examiner asserts that Yuasa et al. disclose compounds which meet the limitations of that instantly claimed in claim 18 wherein R^{21-24} are acetyl groups, R^{25-26} are H, and R^{27} is halogen.

In response to Applicant's amendment of the claim to delimit R^{25} from being halogen, the Examiner states that, since R^{26} or R^{27} can still be halogen, this species is still seen to anticipate the claimed genus and the rejection is maintained.

For the following reasons, the rejection is traversed, respectfully.

Yuasa et al. discloses 4-substituted phenyl α- and β-thioglucopyranosides, particularly mono-halogen substituted phenyl α- and β-5-thioglucopyranosides.

In contrast, the compounds of claim 18 are represented by the following formula (III):



(III)

wherein R^{25} represents an amino group, a C_{2-6} alkanoyl group, a carboxyl group, a formyl group, a C_{2-6} alkoxycarbonyl group or a hydroxyl group.

Therefore, even if R^{26} or R^{27} is a halogen atom, R^{25} is not a hydrogen atom, and thus the compounds of claim 18 do not include mono-halogen substituted β-5-thioglucopyranosides.

Accordingly, claim 18 is not anticipated by Yuasa etal., and the Examiner is requested, respectfully, to remove the rejection.

C. Claim Rejections - Under 35 USC § 103

Claims 1-5, 7-11, 13, and 16-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/74834.

According to the Examiner, the '834 document discloses compounds having the same core, but having an oxygen instead of a sulfur in the sugar ring.

However, the Examiner asserts that the substitution of sulfur for oxygen is seen to be obvious absent unexpected results. The Examiner states that sulfur and oxygen are known ring equivalents and bioisosteres of each other, and compounds only differing in the substitution of one for the other would be expected to have the same properties, and thus produce the same results. As such, the Examiner asserts that it would be obvious to replace the O in the ring of the '834 patent's compounds with S to produce the compounds instantly claimed. The Examiner cites to Silverman et al. for a discussion on bioisosteres.

Claims 1-4, 6-8, 12, 13, and 16-17 are also rejected under 35 U.S.C. § 103(a) as being unpatentable over EPO 850,948.

According to the Examiner, the '948 document discloses compounds having the same core, but having an oxygen in the sugar ring whereas the instant compounds comprise a sulfur in the sugar ring.

However, the Examiner asserts that the substitution of sulfur for oxygen is seen to be obvious absent unexpected results, as discussed above in the context of the rejection over the WO. Accordingly, the Examiner concludes that it would be obvious to replace the O in the ring of the '948 patent's compounds with S to produce the compounds instantly claimed.

For the following reasons, the rejections are traversed, respectfully.

(1) The knowledge that a β-bond between aglycon and glucose was an important structure as an inhibitor of SGLT 2 activity gave rise to a great demand for providing 5-thio-β-D-glucopyranoside derivatives. Prior to the present invention, however, there had been no method of chemical synthesis available for β-selective glycosylation of 5-thioglucose derivatives, and it had been impossible to synthesize aryl 5-thio-β-D-glucopyranoside derivatives. As described in another, commonly owned application (U.S. Appln. No. 10/521,809, now granted as USP 7,250,522), the state of the art at that time was such that aryl 5-thio-β-D-glucopyranoside derivatives could not be synthesized by employing the various reaction conditions then known for glycosylation.

However, the present inventors treated thioaldohexopyranoses under the Mitsunobu reaction conditions that were known to be incapable of causing β-selective glycosylation of 5-thio-L-arabinoses (Carbohydr. Res., vol. 311, p. 191, 1998) and unexpectedly found that the thioaldohexopyranoses underwent β-selective glycosylation to thereby enable selective synthesis of aryl β-thio-β-D-glucopyranoside derivatives.

This finding led to a method of chemical synthesis for β-selective glycosylation of 5-thioglucose derivatives, whereby aryl 5-thio-β-D-glucopyranoside derivatives of formula (i) of the present invention could be synthesized.

Therefore, the aryl 5-thio-β-D-glucopyranoside derivatives of formula (i) of the present invention are new compounds which had not been synthesized before the present inventors successfully achieved the β-selective glycosylation of 5-thioglucose derivatives.

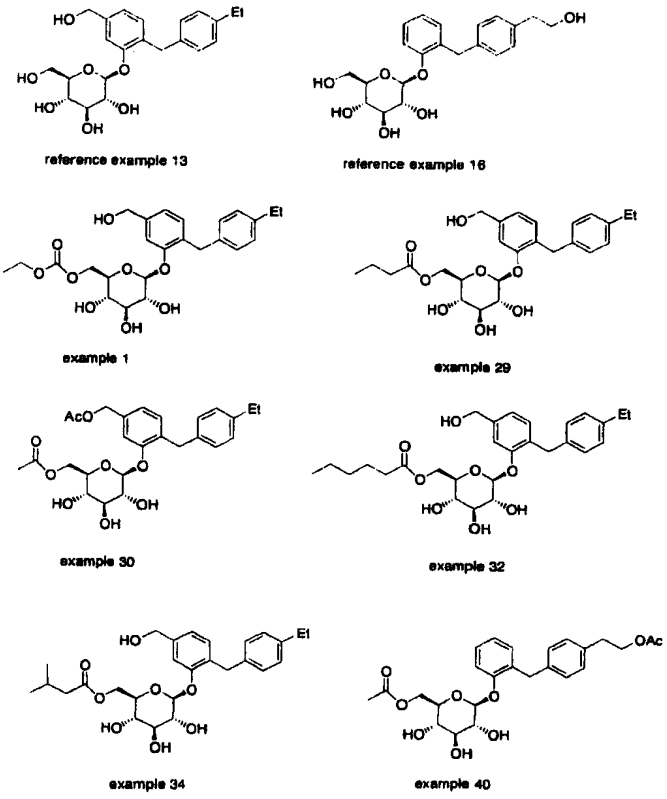
(2) Aryl β-D-glucopyranosides as disclosed in EP 850,948 are easily hydrolyzed at glycosidic linkages by the action of glycosidase present in the small intestine, thus resulting in

low efficiency of their absorption in the unchanged form and in a weak hypoglycemic effect (See the present specification, page 2, lines 2 to 11 and the article in FEBS Letters 436 (1998) 71-75, submitted herewith). The same is true of the compounds disclosed in WO 01/74834 that have a glycosidic linkage. Therefore, aryl β-D-glucopyranosides must be chemically modified to form prodrugs that are stable in vivo. This can be explained by reference to EP 1367060 Al which corresponds to WO 02/064606, cited in the International Search Report.

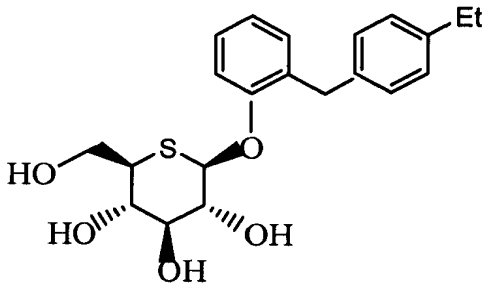
Table 3 of EP 1367060 Al shows that free forms of aryl β-D-glucopyranosides (See the Reference Examples) have bioavailability (%) of 0 and 9 %. In, contrast, the compounds of the Examples are prodrugs and have increased bioavailability (See the structures below).

Test compound	Bioavailability (%)
Example 1	43
Example 29	80
Example 30	65
Example 32	49
Example 34	73
Example 40	65
Reference Example 13	0
Reference Example 16	9

As is clearly shown by the data in Table 3, aryl β-D-glucopyranosides are so unstable in vivo that they must be chemically modified to form prodrugs to have any appreciable bioavailability.



In contrast, the 5-thio-β-D-glucopyranosides of the present claims 1-17 have good bioavailability as evidenced by the data in the executed Rule 132 Declaration submitted herewith. In the declaration, the bioavailability of the compound of Example 24 (Compound 1) of the present invention was determined. As shown in the declaration, this compound had a bioavailability of 61.5%.



WO04/014931: Example 24

Accordingly, unlike the compounds of the cited EP 850,948 and WO 01/74834 , the compounds of present claims 1-17 have good bioavailability without being modified. Therefore, the present compounds have a pharmacokinetic advantage in comparison with the aryl β-D-glucopyranosides disclosed in the cited references.

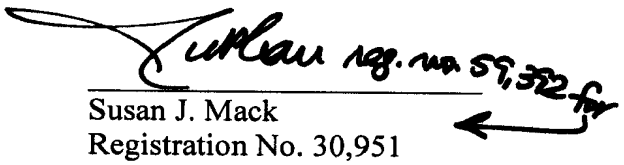
In summary, the aryl 5-thio-β-D-glucopyranoside compounds of the presently claimed compounds could not have been synthesized by employing the various reaction conditions that were known for glycosylation and used for synthesis of the aryl β-D-glucopyranosides disclosed in the prior art; and the presently claimed compounds have advantageous effects over the aryl β-D-glucopyranosides disclosed in the cited references. Therefore, the presently claimed compounds are not made obvious over the cited references.

In view of the above remarks and data submitted in the Rule 132 Declaration, the Examiner is requested, respectfully, to reconsider and remove the obviousness rejections.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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